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1637

Atty. Docket No.: 22620/1222 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Murchie, et al.	Examiner:	S. Chunduru
Serial No.:	09/839,649		
Filed:	April 19, 2001	Group Art Unit:	1637
Entitled:	"Assay for Identification of a Test Compound"	Conf. No.:	2120

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8a

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Kathleen Williams
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Commissioner for Patents
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TRANSMITTAL LETTER

Enclosed for filing in the above-identified patent application, please find the following documents:

1. Response to Office Action mailed June 27, 2003;
2. Statement of Substance of Examiner Interview;
3. Petition for Extension of Time;
4. Check in the amount of $475.00 for the requisite fee; and
5. Return Post Card.

The Commissioner for Patents is hereby authorized to charge any deficiencies or credit any overpayment in the total fees to Deposit Account No. 16-0085, Reference No. 22620/1222. A duplicate of this transmittal letter is enclosed for this purpose.

Respectfully submitted,

Date: December 5, 2003

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STATEMENT OF SUBSTANCE OF EXAMINER INTERVIEW

Sir:

Applicants hereby submit a complete written statement as to the substance of a telephone interview between Examiner S. Chunduru and Applicants' attorneys (Barbara A. Gyure and Cynthia Zhang) on December 3, 2003, in compliance with 37 C.F.R. § 1.133(b), and MPEP §§ 502.03 and 713.01. Claims 1-13 and 16 were discussed during the interview, as well as the outstanding rejections under 35 U.S.C. Sections 112(b), 102 and 103, as detailed below. As this was a telephonic interview, there were no exhibits or demonstrations.

The participants initially discussed the indefiniteness rejection (Section 112, second paragraph) based on the use of the term "suicide substrate," which the Examiner alleges is indefinite since it is unclear "whether it refers to a specific inhibitor region, an apoptotic site, an enzyme suppressor region, or a mutant substrate region of the target RNA." Applicants' attorneys explained that no amendment to the claims is necessary, since the term "suicide substrate" is clearly defined in the specification as "an enzyme substrate, e.g., a target RNA or a nucleotide or base within the target RNA, that when modified by the enzyme, irreversibly binds to and inhibits the further activity of the enzyme" (see page 13, line 29, through page 14, line 1). Thus, as will be appreciated by one of skill in the art, the suicide substrate is an enzyme inhibitor

or inactivator, which functions by irreversibly binding to and preventing further enzymatic activity. Because of this definition, the term cannot mean "an apoptotic site" or other active site on the RNA. Hence, there will be no confusion on the part of the skilled artisan as to the meaning of this term. The skilled artisan will understand that "suicide substrate" in claim 16 means a particular type of substrate, i.e., one which inhibits or inactivates the enzyme.

Next, the participants discussed the rejection of claims 1-11 under 35 U.S.C 102(b) based on Hansen et al., *RNA*, 5: 93-101 (1999). The Applicants' attorneys explained to Examiner Chunduru that the reference does not teach every element of the claims, as required of an anticipatory reference. Specifically, the Applicants' attorneys pointed out that the Hansen et al. reference does not teach a method for determining whether a test compound binds to a target RNA, as required by independent claim 1, and hence claims 2-11, which depend therefrom. Nowhere in this reference is there any teaching or suggestion of combining the three components (test compound, target RNA and RNA-modifying enzyme) in a single vial, thereby "contacting" these elements, as required by Applicants' claims. Rather, the Hansen et al. reference teaches the correlation between the methylation fidelity in *E. coli* 23S rRNA and the magnesium concentration in the medium. In a separate parallel experiment, the chemical agents DMS and Kethoxal are mixed with RNA (without enzyme) to evaluate the 23S rRNA secondary structures. In other words, DMS and kethoxal, which are known in the art to modify the unpaired bases on the secondary structure, are used to aid in determining the structure of 23S rRNA. Hansen et al. further teach that under standard physiological conditions, the ErmE methyltransferases specifically methylate adenine at position 2058 in *E. coli* 23S rRNA. However, as the magnesium concentration decreases, more adenine sites in *E. coli* 23S rRNA are methylated by ErmE methyltransferases. The 23S rRNA structures unfold on depletion of magnesium, making more adenine sites accessible for ErmE methyltransferases modification. Again, nowhere in this reference is there any teaching or suggestion to combine (i.e., "contact") the test compound, target RNA, and RNA-modifying enzyme, nor is there any teaching or suggestion of a method for determining whether a test compound binds to a target RNA, as claimed by Applicants.

Examiner Chunduru and the Applicants' attorneys then discussed the rejection of claims 1-7, 9, 11 based on Schwarts et al. (U.S. Pat. No. 6,020,149). Applicants attorneys argued that

the Schwarts et al. reference fails to teach "the binding of the test compound with the target RNA," as required by Applicants' claims. Rather, Schwarts et al. teaches (1) a SAM-mediated methyl transferase (a target modifying enzyme) that methylates a target substrate such as RNA (target RNA), whereas S-adenosylhomocysteine (SAH), a product resulting from the SAM-mediated methylation process, acts as a differential inhibitor of SAM-mediated methylation (see col. 15, lines 16-65). Schwarts et al. teaches a method of evaluating the impact of a test compound on a target cellular process characteristic of a disease or condition. Thus, although Schwarts et al. teaches individual components of Applicants methods, the reference does not teach inhibition of an RNA-modifying enzyme (SAM-mediated methyl transferase) by the test compound via binding of the compound to the target RNA. Nor is such binding inherent in the Schwarts et al. reference, since it neither necessarily nor "naturally results" from the disclosed method. In support of their position, Applicants' attorneys discussed Yi, P. et al., *J. Bio. Chem.*, 275(38): 29318–29323 (2002). The Yi et al. reference teaches that SAH inhibits the SAM-mediated methyltransferase by binding to the SAM-mediated methyltransferase, not to the target RNA.

Next, the participants discussed the Section 102 rejection of claims 1-4 and 16 based on Glazer et al., *J. Biol. Chem.*, 259(21):12964-12969. Applicants' attorneys argued that this reference also fails to teach every element of the claims, namely that NPC ("test compound") inhibits RNA methylation via binding to the target RNA. Applicants attorneys explained that NPC inhibits methylation through binding to S-adenosylhomocysteine hydrolase, an enzyme that does **not** modify RNA, but rather is involved in regulating methytransferase (RNA modifying enzyme) activity. Applicants attorneys further discussed Borchardt, RT et al., "Neplanocin A, a potent inhibitor of S-adenosylhomocysteine hydrolase and of vaccinia virus," *J. Bio. Chem.*, 259(7): 4353-4358 (1984), which teaches that NPC inhibits S-adenosylhomocysteine hydrolase (SAAH) by binding to SAAH, and the binding is related to inhibition of S-adenosylmethionine(SAM)-dependent methylation of RNA. As in known in the art, SAAH promotes methylation by cleaving a byproduct of all S-adenosymethionine (SAM)-dependent methylation reactions, whereas the byproduct inhibits the methylation reactions by binding to SAM-mediated methyltranferases, and that the inhibition of the SAAH enzymatic activity by NPC serves to inhibit the methylation reactions. Thus, NPC does not inhibit methylation by

binding to the target RNA, rather, it inhibits methylation by binding to SAAH, an **non**-RNA-modifying enzyme.

Finally, the participants discussed the rejection of claims 12 and 13 under 35 U.S.C. §103(a) based on Hansen et al. in view of Karn et al. (U.S. Pat. No. 6,316,194). Applicants' attorneys argued that the examiner had failed to establish a *prima facie* case of obviousness, because, as discussed above, Hansen et al. does not teach a method for determining whether a test compound binds to a target RNA, nor does it even teach combining (i.e., "contacting") the three components in a single vial. Instead, Hansen et al. teaches a correlation between the methylation fidelity in *E. coli* 23S rRNA and the magnesium concentration in the medium. Thus, the Hansen et al. reference fails to teach or suggest the claimed invention nor does the secondary reference (Karn et al.) supply the deficiencies.

Although no agreement was reached between the Examiner and the Applicants' attorneys, Examiner Chunduru stated that the arguments "sound good" and that in her opinion the rejections "can be withdrawn." However, the Examiner indicated that she must discuss the rejections with her supervisor before she can issue a Notice of Allowance. Finally, the Examiner agreed to reconsider the rejections based on the above arguments, as well as any arguments Applicants may present in their written reply to the outstanding Office Action.

It is believed that no fees are due. However, if overlooked, the Commissioner for Patents is hereby authorized to charge all fees in the total amount to Deposit Account 16-0085, Reference No. 22620/1222.

Respectfully submitted,

Date: December 5, 2003

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